

**REMARKS**

**I. Status of the Claims**

Reconsideration of the present application is respectfully requested. Claims 1-4, 7-16, 19-31, 33-37 and 39 are currently pending. Claims 5-6, 17, 18, 32 and 38 have been previously canceled without prejudice. No new matter has been introduced into the claims.

**II. Rejections Under 35 U.S.C. §103(a)**

Claims 1-4, 7-16, 19-31, 33-37, and 39 stand rejected under 35 U.S.C. 103(a) as obvious over U.S. Patent No. 5,688,516 (to Raad et al.) in view of Domenico et al. (Journal of Antimicrobial Chemotherapy, 28(6):801-810,1991), International Publication No. WO 97/25085 (to Modak et al.), and U.S. Patent No. 6,719,991 (to Darouiche et al.). The Examiner contends that Raad describes a combination of antimicrobials (e.g., minocycline), and chelators (e.g., zinc citrate, citrate and bismuth), which are effective antimicrobials against Staphylococci and Candida attached to medical devices, and further, are effective for inhibiting the formation of glycocalyx by the microorganisms which facilitate their attachment to the medical devices. Additionally, according to the Examiner, Domenico discloses that bismuth ions and salicylate ions, when combined, have an additive effect on inhibiting bacterial growth. The Examiner also alleges that Modak describes treating polymeric medical articles, such as vascular catheters, with chlorhexidine compounds, silver sulfadiazine and benzalkonium chloride, and further, that Darouiche discloses the combination of an antibiotic, such as minocycline, and an antiseptic, such as chlorhexidine, triclosan or silver, for coating catheters. The Examiner contends that the elements disclosed by the prior art are useful for the same purpose (*i.e.*, as antimicrobial agents), and thus it is *prima facie* obvious to combine the elements of the cited references together in a new composition to be used for the same purpose. According to the Examiner, such a combination of the elements of the cited art renders the claims obvious.

Applicants respectfully traverse the rejection and submit that the present claims are not obvious over the cited art. Evidence of unobvious or unexpected advantageous properties rebuts *prima facie* obviousness, and the presence of a property not possessed by the prior art is sufficient evidence of non-obviousness. *See* M.P.E.P. 716.02(a); *see also* *In re Papesch*, 315 F.2d 381 (C.C.P.A. 1963). The claimed invention encompasses, *inter alia*, the unexpected

discovery that the antiseptic and antibiotic agents of the claimed invention, when combined, exhibit a synergistic increase in their combined antimicrobial efficacy and/or are effective in reducing the development of antibiotic resistant microorganisms.

As disclosed in the Example at pages 10-14 of the instant application, a composition comprising both the antiseptic triclosan and the antibiotic minocycline exhibited an unexpected increase in antimicrobial effectiveness against *S. epidermidis* cultures, which was greater than the additive effect of each agent's independent antimicrobial activity (*i.e.*, a synergistic antimicrobial effect). *See* the specification at pages 13-14. Specifically, a composition comprising both agents could achieve the same antimicrobial effectiveness against the bacterial culture at a lower concentration than the combined amounts of two independent compositions comprising triclosan or minocycline. *See* the specification at page 13, Table III (8.35% of the combined independent effective concentrations of triclosan and minocycline was equally effective against *S. epidermidis* when the agents were used in a single composition.). Based on these discoveries, the specification discloses the following:

In conclusion . . . minocycline w[as] observed to exhibit synergy in combination with . . . triclosan, in addition to having lower increases in MIC after 20 passages through sub-inhibitory concentrations *in vitro* . . .

*See* the specification at page 14, lines 1-7. Additionally, synergistic antimicrobial effects were also observed when minocycline was combined with triclosan and a bismuth salt (*i.e.* bismuth nitrate). *See* the specification at page 24, Table X (A composition comprising bismuth nitrate alone, and a composition comprising triclosan and minocycline both produced no zone of inhibition on a lawn of *P. aeruginosa*. When all three agents were combined in a single composition, a 15 mm zone of inhibition was induced on the lawn.).

Applicants submit that none of the cited references suggest or describe that triclosan and minocycline, when combined together in a single composition, exhibit a synergistic antimicrobial effect. Applicants' discovery of such an unexpected result is indicative of the claims' non-obviousness in view of the prior art.

Furthermore, Applicants submit that a similar unexpected synergistic increase in antimicrobial activity was observed when minocycline was combined with other antimicrobial agents of the claimed invention. For example, as shown in the Examples on pages 31-35, a composition comprising minocycline and any one of nine different bismuth salts, for example,

bismuth citrate or bismuth salicylate, exhibited a synergistic increase in antimicrobial activity that was greater than the additive effect of the agents' independent activities. See the specification at Tables XV and XVI (Minocycline and eight of the nine bismuth salts tested induced no zone of inhibition on a lawn of *P. aeruginosa* when tested independently. One bismuth salt, bismuth sulfadiazine, induced a 6 mm zone of inhibition. When minocycline and each bismuth salt were formulated in single compositions (*i.e.*, minocycline and one bismuth salt per composition), a zone of inhibition from 15 mm to 18 mm was observed.).

Similarly, a composition comprising benzalkonium chloride ("BZK"), minocycline, and bismuth nitrate exhibited a synergistic increase in antimicrobial effectiveness against *S. epidermidis*. As shown in the Example at pages 26-28, a composition formulated with any two of BZK, minocycline, and bismuth nitrate, exhibited an antimicrobial effectiveness similar to a composition comprising only BZK. See the specification at p. 28, Table XIII (a composition comprising the antimicrobial agent(s) BZK; BZK and bismuth nitrate; minocycline and bismuth nitrate; or BZK and minocycline, exhibited antimicrobial activities sufficient to reduce bacterial cultures to 100 colony forming units ("cfu")/mm<sup>2</sup>; 90 cfu/mm<sup>2</sup>; 200 cfu/mm<sup>2</sup>; and 100 cfu/mm<sup>2</sup>, respectively.). However, when all three agents were combined in a single composition, the number of cfu/mm<sup>2</sup> was reduced to only 2.5, demonstrating a synergistic effect between the three antimicrobial agents.

In addition to the surprising synergistic effects described above, the antibiotic/antiseptic combinations encompassed by the claims of the instant invention exhibited an unexpected effectiveness against the development of antibiotic resistant microorganisms. As described in the specification, skilled artisans had previously attempted to prevent the development of resistance to antibiotic coated catheters by impregnating the catheters with two antibiotics having different mechanisms of action, for example, minocycline and rifampin. However, microorganisms continued to develop resistance to the two antibiotics. In the instant application, Applicants have unexpectedly discovered that a combination of an antibiotic (*i.e.*, minocycline) and an antiseptic, as encompassed by the claimed invention, inhibited microorganisms from developing such an antibiotic resistance. See the specification at page 9, lines 4-13. For example, as disclosed in Table IIA of the specification (see page 12), the minimum inhibitory concentration ("MIC") of minocycline and chlorhexidine diacetate effective to prevent *S. epidermidis* growth increased two fold after cultures of the bacteria were subjected to 20-25

passes through subinhibitory doses of either antimicrobial agent. In contrast, when minocycline and chlorhexidine were combined in a single composition, the MIC increased only 1.66 fold following 20-25 passes. Furthermore, catheters impregnated with both minocycline and chlorhexidine maintained a greater antimicrobial effectiveness against bacteria over longer periods of time compared to catheters comprising only minocycline or chlorhexidine. *See* the specification at page 38, Table XIX; page 41, Table XXI; and page 43, Table XXIII.

In addition to reducing the development of antimicrobial resistance, a compound comprising both minocycline and chlorhexidine also exhibited an unexpected synergistic antimicrobial activity. While minocycline alone was ineffective against *P. aeruginosa*, and chlorhexidine could induce only a 10 mm zone of inhibition on a lawn of *P. aeruginosa*, a composition comprising both minocycline and chlorhexidine exhibited an antimicrobial activity effective to produce an 11 mm zone of inhibition on a lawn of *P. aeruginosa*, demonstrating a synergistic increase over the independent effects of the two agents. *See* the specification at page 33, Table XV; page 25, Table XI; and pages 36-37, Table XVII.

As described above, the compounds encompassed by the claims of the instant invention have been shown to exhibit unexpected results with regard to their synergistic antimicrobial activity, and further, their ability to inhibit the development of antibiotic resistance. Such surprising results support the non-obviousness of the present claims over the cited art. Therefore, Applicants respectfully request that the rejections be withdrawn.

### **III. Double Patenting**

Claims 1-4, 7-16, 19-31, 33-37 and 39 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-55 of U.S. Patent No. 6,106,505 (“the ‘505 patent) and claims 1-15 of U.S. Patent No. 6,582,719 (“the ‘719 patent”) in view of Raad, Domenico, Modak and Darouiche. The Examiner contends that claims 1-55 of the ‘505 patent are directed to an anti-infective medical article, such as an intravenous catheter, which has been impregnated with chlorhexidine free base and triclosan, and can further comprise silver sulfadiazine. According to the Examiner, in view of Raad, Domenico, Modak and Darouiche, it would have been obvious to modify the medical article of the ‘505 patent to comprise minocycline and chlorhexidine; minocycline, triclosan and bismuth; or minocycline and bismuth.

With regard to claims 1-15 of the '719 patent, the Examiner alleges that the claims of the '719 patent encompass a medical article impregnated with the antibiotics and antiseptics of the instant claims except for the agents bismuth citrate, bismuth salicylate, chlorhexidine gluconate and zinc salt. According to the Examiner, in view of Raad, Domenico and Modak, it would have been obvious for a skilled artisan to modify the medical article of the '719 patent to include such agents.

Without conceding to the Examiner's contentions, Applicants respectfully submit that the appropriate action will be taken (*e.g.*, through the submission of a Terminal Disclaimer), as the Examiner indicates allowable subject matter in the instant application.

#### **IV. Conclusion**

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue. If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below. Applicants believe that aside from the fee for the Request for Continued Examination, no additional fees are due. If however additional fees are due, the Commissioner is hereby authorized to charge payment of fees or to credit any overpayment associated with this communication to Deposit Account No. 02-4377.

Respectfully submitted,

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Date: 8/28/18

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